Complete Summary

GUIDELINE TITLE

EFNS guidelines on management of narcolepsy.

BIBLIOGRAPHIC SOURCE(S)

Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, Mayer G, Pollmacher T, Reading P, Sonka K, EFNS Task Force. EFNS guidelines on management of narcolepsy. Eur J Neurol 2006 Oct;13(10):1035-48. [90 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

An update of the guidelines will need to be considered if sodium oxybate is registered for 'narcolepsy' and once sodium oxybate has been used for cataplexy, for two years or so.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- October 24, 2007, Provigil (modafinil): Cephalon has agreed to include additional labeling revisions to the WARNINGS, CLINICAL PHARMACOLOGY, PRECAUTIONS, and PATIENT PACKAGE INSERT sections.
- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.
- May 12, 2006, Paxil (paroxetine) and Paxil CR: Changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section in the prescribing Information related to adult patients, particularly those who are younger adults.
- December 8, 2005, Paxil (paroxetine): Pregnancy category changed from C to D and new data and recommendations added to the WARNINGS section of prescribing information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Narcolepsy

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pharmacology
Pulmonary Medicine
Sleep Medicine

INTENDED USERS

Physicians
Social Workers

GUIDELINE OBJECTIVE(S)

To reinforce the use of those drugs evaluated in randomized placebo-controlled trials and to reach a consensus, as much as possible, on the use of other available medications

TARGET POPULATION

Patients suffering from narcolepsy with and without cataplexy

INTERVENTIONS AND PRACTICES CONSIDERED

Management

1. Complete interview, all-night polysomnography, and multiple sleep latency test (MSLT), cerebrospinal fluid hypcretin-1 measurement
2. Patient education about their condition, available medications, and their potential side effects
3. Pharmacological treatment
    - Excessive daytime sleepiness and irresistible episodes of sleep: modafinil, methylphenidate, sodium oxybate, behavioral treatment
    - Cataplexy, hallucinations and sleep paralysis: sodium oxybate, antidepressants, avoidance of triggers
    - Poor sleep: benzodiazepines or non-benzodiazepine hypnotics, modafinil, sodium oxybate
    - Parasomnia: conventional medications
    - Treatment of features associated with narcolepsy
4. Psychosocial support and counseling
5. Regular follow-up

Note: Refer to the original guideline document for other available medications. Given the availability of modafinil and methylphenidate, and the foreseen registration of sodium oxybate for narcolepsy (including excessive daytime sleepiness, cataplexy, disturbed nocturnal sleep) in Europe, the place of other compounds will become fairly limited.

MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment in terms of reduced daytime sleepiness, irresistible episodes of sleep, and cataplectic attacks; increased sleep latencies; improved sleep efficiency and overall sleep quality
- Adverse effects of medications
- Features associated with narcolepsy (obstructive sleep apnea, periodic limb movement in sleep, depression)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Several databases were used including Cochrane library, MEDLINE, EMBASE, Clinical Trials until September 2005. Previous guidelines for treatment were sought. Each member of the Task Force was assigned a special task, primarily based on symptoms of narcolepsy (excessive daytime sleepiness and irresistible episodes of sleep, cataplexy, hallucinations and sleep paralysis, disturbed nocturnal sleep, parasomnias) and also on associated features (obstructive sleep apnea, adult periodic limb movements in sleep [PLMS], neuropsychiatric symptoms) and special treatments (behavioral and experimental). The best

available evidence to address each question was sought, with the classification scheme by type of study design according to the European Federation of Neurological Societies (EFNS) Guidance document. If the highest level of evidence was not sufficient or required updating the literature search was extended to the lower adjacent level of evidence.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A Task Force composed of the leading specialists of narcolepsy in Europe has been appointed. Each member of the Task Force was first invited to send his own contribution to the chairman. Then a meeting gathering seven of the nine members of the Task Force was scheduled during the 5th International Symposium on Narcolepsy in Ascona, Switzerland, October 10–15, 2004. A draft of the Guidelines was then prepared by the chairman and circulated amongst all members of the Task Force for comments. On receipt of these comments the chairman prepared the final version which was circulated again amongst members for endorsement.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points Where there was a lack of evidence but consensus was clear, the Task Force has stated their opinion as good practice points.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see "Availability of Companion Documents" field in this summary).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Points) are defined at the end of the "Major Recommendations" field.

Excessive Daytime Sleepiness and Irresistible Episodes of Sleep

First-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep should rely on modafinil, 100 to 400 mg/day, given in two doses, one in the morning and one early in the afternoon (**level A**). In a few cases dosage should be increased up to 300 mg twice a day. Increase of the daily dosage above 600 mg is in general not advisable. Second line pharmacological treatment is methylphenidate at a daily dosage of 10–60 mg. Of note a growing practice in the USA, based on **level A** evidence, of using sodium oxybate as a first line treatment of excessive daytime sleepiness. This could be the case in Europe as well, if sodium oxybate is registered for narcolepsy (including cataplexy, excessive daytime sleepiness and disturbed nocturnal sleep). In severe cases the combination of modafinil and sodium oxybate appears to be beneficial. Given these various possibilities the role of other compounds becomes fairly limited, unless recommended treatments have failed. Behavioral treatment measures are always advisable. Essentially the studies available support on a **B level** the recommendation to take planned naps during the day, as naps decrease sleep tendency and shorten reaction time. Because of varying performance demands and limitations on work or home times for taking them, naps are best scheduled on a patient-by-patient basis.

Cataplexy

Based on **class I evidence** (**level A rating**) studies, first-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum dosage of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g. Most patients will start to feel better within the first few days, but optimal response at any given dose may take as long as 8 to 12 weeks. For this reason adjustment should typically occur at least at 2-week intervals. Second-line pharmacological treatments are antidepressants. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are the most potent anticataplectic drugs. However they have the drawback of anticholinergic adverse effects. Starting dosage should be as low as possible. Selective serotonin re-uptake inhibitors (SSRIs) are slightly less active but have less adverse effects. The norepinephrine/serotonin reuptake inhibitor venlafaxine is widely used today but lacks any published clinical evidence of efficacy. Norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, also lack published clinical evidence. Given the availability of sodium oxybate and the activity of antidepressants, the place for other compounds is fairly limited. There is no accepted behavioral treatment of cataplexy. However, advice to some subjects should include the avoidance of known triggers, whenever possible.

Hallucinations and Sleep Paralysis

As for cataplexy but there is a lack of studies with these outcome parameters.

Poor Sleep

Benzodiazepines or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep (**level C**). Objective evidence is lacking over intermediate or long-term follow-up. The improvement reported by some patients once established on modafinil is noteworthy. According to **level A** studies with gamma-hydroxybutyrate and sodium oxybate, sodium oxybate might become the most appropriate option.

Parasomnias

Based on available information it is difficult to provide guidance for prescribing in parasomnias associated with narcolepsy other than to recommend conventional medications.

Associated Features

Obstructive sleep apnea (OSA) should be treated no differently to the general population, although some experts have the experience that the majority of patients refuse to continue continuous positive airway pressure (CPAP) therapy because of a lack of clinical improvement. There is usually no need to treat periodic limb movements in sleep (PLMS) in narcoleptic patients. Antidepressants and/or psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients.

Psychosocial Support and Counseling

Interaction with narcoleptic patients and counseling from trained social workers are recommended (**level C**).

Good Practice Points

A prerequisite before implementing a potentially lifelong treatment is to establish an accurate diagnosis of narcolepsy with or without cataplexy, and to check for possible comorbidity. Following a complete interview the patient should undergo an all-night polysomnography followed immediately by a multiple sleep latency test (MSLT). Human leucocyte antigen (HLA) typing is rarely helpful. Cerebrospinal fluid (CSF) hypocretin-1 measurement may be of help and is added as diagnostic test in the revised International Classification of Sleep Disorders, particularly if the MSLT cannot be used or provides conflicting information. Levels of CSF hypocretin are only significantly reduced or absent in cases of narcolepsy with cataplexy. In the absence of cataplexy, the value of measuring hypocretin is debatable.

Once diagnosed, patients must be given as much information as possible about their condition (nature of the disorder, genetic implication, medications available

and their potential adverse effects) to help them cope with a potentially debilitating condition.

Regular follow-up is essential to monitor response to treatment, adapt the treatment in case of insufficient response or adverse effects, and above all encourage the patient to stand on an efficacious therapy. Another polysomnographic evaluation of patients should be considered in case of worsening of symptoms or development of other symptoms, but not for evaluating treatment in general.

Definitions:

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Rating of Recommendations

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Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points Where there was a lack of evidence but consensus was clear, the Task Force has stated their opinion as good practice points.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of narcolepsy

POTENTIAL HARMS

Adverse Effects of Medications

- Modafinil is associated with headache, nausea, and rhinitis. On rare occasions worsening of cataplexy has been observed.
- Adverse effects of methylphenidate are the same as with amphetamines (i.e. minor irritability, hyperactivity, mood changes, headache, palpitations, sweating, tremors, anorexia, and insomnia). However methylphenidate probably has a better therapeutic index than dextro-amphetamine with less reduction of appetite or increase in blood pressure. Tolerance may develop.
- Most commonly reported adverse effects of and sodium oxybate are nausea, which usually goes away after a few days, nocturnal enuresis which may persist intermittently, confusional arousals, and headache. Of concern is the abuse potential of sodium oxybate/gamma-hydroxybutyrate (GHB).
- Clomipramine is associated with anticholinergic effects including dry mouth, sweating, constipation, tachycardia, weight increase, hypotension, difficulty in urinating, and impotence. Patients may experience with tricyclics a worsening or 'de novo' onset of rapid eye movement (REM) sleep behavior disorder (RBD). Moreover, there is a risk, if the tricyclics are suddenly withdrawn, of a marked increase in number and severity of cataplectic attacks, a situation referred to as 'rebound cataplexy', or even 'status cataplecticus'. Tolerance to the effects of tricyclics may develop. If cataplexy is mild, it is advisable to cease the anti-cataplectic drug before conception.
- Adverse effects of selective serotonin re-uptake inhibitors (SSRI) are less pronounced than with tricyclics. They include central nervous system excitation, gastrointestinal upset, movement disorders and sexual difficulties. The risk of marked increase in number and severity of cataplectic attacks has been documented after discontinuation of SSRIs.

Refer to the original guideline document for more information on adverse effects of these and other drugs.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Use of methylphenidate is contraindicated in pregnancy
- Modafinil, sodium oxybate, and selective serotonin re-uptake inhibitors (SSRIs) are not recommended during pregnancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.
- The recommendations expressed in these guidelines are based on the best currently available knowledge. However, developments in the field of narcolepsy are rapidly advancing and the use of agents such as sodium oxybate may become widespread, largely depending on regulation issues. In addition, treatments directed at replacing hypocretin or even preventing the loss of neurons containing the neuropeptide may become a reality in the near future.
- An update of the guidelines will need to be considered if sodium oxybate is registered for 'narcolepsy' (including excessive daytime sleepiness and disturbed nocturnal sleep in addition to cataplexy) and once sodium oxybate has been used for cataplexy, for two years or so. The introduction on the market of one of the future experimental therapies listed at the end of the Guidelines may well have a profound impact on subsequent recommendations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, Mayer G, Pollmacher T, Reading P, Sonka K, EFNS Task Force. EFNS guidelines on management of narcolepsy. Eur J Neurol 2006 Oct;13(10):1035-48. [90 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Oct

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on the Management of Narcolepsy

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: M. Billiard, School of Medicine, University of Montpellier, Montpellier, France; C. Bassetti, Neurology Department, University Hospital, Zurich, Switzerland; Y. Dauvilliers, Neurology Department, Gui de Chauliac Hospital, Montpellier, France; L. Dolenc-Groselj, Institute of Clinical Neurophysiology, Division of Neurology, University Medical Center, Ljubljana, Slovenia; G. J. Lammers, Department of Neurology and Clinical Neurophysiology, Leiden University, Medical Center, Leiden, The Netherlands; G. Mayer, Hephata Klinik, Department of Neurology, Schwalmstadt-Treysa, Germany; T. Pollmächer, Zentrum für Psychiatrie und Psychotherapie, Klinikum Ingolstadt, Ingolstadt, Germany; P. Reading, The James Cook University Hospital, Middlesbrough, UK; K. Sonka, Department of Neurology, Charles University, Prague, Czech Republic

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr Billiard received honoraria from Orphan Drugs for invited talks and is a member of the Xyrem (UCB Pharma) advisory board.

Dr Bassetti received honoraria from Orphan Drugs for invited talks and is a member of the Xyrem (UCB Pharma) advisory board. He was involved in clinical trials with Cephalon and Orphan.

Dr Dauvilliers was involved in a clinical trial with Cephalon and another one with Orphan.

Dr Lammers is a member of the Narcolepsy advisory group for Organon Nederland BV (license holder for modafinil in the Netherlands) and a member of the Xyrem (UCB Pharma) advisory board.

Dr Mayer received honoraria from Cephalon and UCB Pharma for invited talks. He was involved in one trial with Cephalon and two trials with Orphan Drugs. He is a member of the Xyrem advisory board.

Dr Reading received honoraria from Cephalon for invited talks. Dr Sonka was involved in two trials with Orphan and is currently involved in a trial with Cephalon.

Dr Sonka is also a member of the Xyrem advisory board.

GUIDELINE STATUS

This is the current release of the guideline.

An update of the guidelines will need to be considered if sodium oxybate is registered for 'narcolepsy' and once sodium oxybate has been used for cataplexy, for two years or so.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from M. Billiard, School of Medicine, University of Montpellier, Montpellier, France; Phone: 33 675 02 83 64; Fax: 33 4 67 66 1862; E-mail: mbilliard@wanadoo.fr

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.
- Continuing Medical Education questions available from the European Journal of Neurology Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 11, 2007. The information was verified by the guideline developer on May 25, 2007. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Provigil (modafinil) Tablets. This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs.

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